REMARKS

At the outset, Applicant wishes to thank Examiners Natarajan and Helms for the courtesy of a telephonic interview on May 8, 2008. During the interview, amendments to the claims were proposed to clarify the claimed subject matter. The Examiners' suggestions and guidance in this regard are greatly appreciated.

The participants in the teleconference included Examiner Meera Natarajan, Ph.D., Examiner Larry Helms, Ph.D., Robert Wieder, M.D. (inventor), and Sarah J. Fashena, Ph.D. (Agent for Applicant). During the interview, novel and non-obvious aspects of the invention were discussed. Amendments to the claims were also discussed with respect to clarification of the claimed subject matter. The Examiners' assistance in this regard is greatly appreciated.

Claims 1, 5, 7-12, 47, and 50-59 are pending. Claims 7, 8, 10, 11, 47, 50-52, and 55-59 are withdrawn from consideration and are canceled herein without prejudice. Claims 1 and 12 are amended herein to more clearly set forth aspects of the invention. New claims 60 and 61 are presented herein. Accordingly, instant claims 1, 5, 9, 12, 53, 54, 60, and 61 are under consideration.

Support for the amendments to the claims is found throughout the specification and in the original claims. Specifically, support for the amendment to claims 1 and 12 is presented in original claims 2, 12, and 54 and, for example, at paragraphs [0019], [0020], [0022], [0082], [0114], and [0116], wherein support for practicing the method of the invention in a mammal with breast cancer is found. No issue of new matter is introduced by the amendments to the claims.

Support for the new claims is found throughout the specification and in the original claims. Specifically, support for new claims 60 and 61 is presented in original claims 1, 2, 12, and 54 and, for example, at paragraphs [0114] and [0116], wherein support for practicing the method of the invention in a human is found. No issue of new matter is introduced by the amendments to the claims.

Rejections under 35 USC § 102

Claims 1, 5, 9, 12, 53, and 54 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Nista et al. (1997, Int J Cancer 72:133-141). In view of the amendments to

the claims and Applicant's arguments presented herein, the rejection, as it applied to claims 1, 5, 9, 12, 53, and 54, is respectfully traversed.

The claims are amended herein to be directed to a method for disrupting survival signaling from a bone marrow microenvironment to single breast cancer cells or breast cancer cell micrometastases in a mammal with breast cancer, said method comprising administering to said mammal with breast cancer (claim 1) or a method of inhibiting cellular proliferation or inducing cell death or cellular differentiation of single breast cancer cells or breast cancer cell micrometastases in a mammal with breast cancer or for treating a single breast cancer cell or breast cancer micrometastases in a mammal with breast cancer comprising administering to the mammal with breast cancer (claim 12), either of said methods comprising administering an agent effective in blocking the interaction of an integrin with an extracellular matrix protein of the bone marrow microenvironment, wherein the integrin is alpha 5 beta 1 and the extracellular matrix protein is fibronectin.

In contrast, Nista et al. fail to teach or suggest the recited methods of claims 1 or 12, which call for administering to a mammal with breast cancer an agent effective in blocking the interaction of an integrin with an extracellular matrix protein of the bone marrow microenvironment, wherein the integrin is alpha 5 beta 1 and the extracellular matrix protein is fibronectin. Indeed, the prior art, including that of Nista et al., teaches that breast cancer cells do not express integrins and would therefore not be inhibited by blocking interactions with structural proteins such as fibronectin. Support for this assertion is found in Figures 1 and 2, wherein Nista et al. demonstrate very clearly that MCF-7 cells do not express integrin $\alpha5\beta1$ because they do not express integrin $\alpha5$. Moreover, because of the lack of expression of integrin $\alpha5\beta1$ or integrin $\alpha4\beta1$ by MCF-7 cells, their minimal adhesion to fibronectin is not dependent on integrin binding, as demonstrated by lack of reversal by an RGD peptide (Nista et al., Figure 3). A skilled practitioner would appreciate that the MCF-7 cells are understood to be representative of breast cancer cells *in vivo* with respect to integrin expression. That being the case, the Nista et al. reference fails to teach at least one recited element of the claims, namely administering the recited agents to a mammal with breast cancer. Nor does the Nista et al. reference present any motivation to attempt the claimed method.

Moreover, Nista et al. actually teaches away from the present invention because this reference presents evidence that breast cancer cells, as typified by MCF-7 cells, do not express integrins and would, therefore, not be affected by agents that block integrin binding. In contrast, Nista et al. focus their study on the ADR^R MCF-7 cell line, which is a cell line artificially derived to have adriamycin resistance. As previously stated, this artificially created cell line is not representative of breast cancer cells in patients. Additional details relating to breast cancer cells in patients are presented below.

The analysis of the ADR^R MCF-7 cell line performed by Nista et al. demonstrates that this artificially derived cell line re-expresses integrins $\alpha5\beta1$ and $\alpha4\beta1$ and is dependent on these integrins for adhesion, proliferation and survival (Nista et al., Figure 3). The inhibition mediated by the RGD-containing peptide was only observed for the ADR^R MCF-7 cell line. Knowing that the ADR^R MCF-7 cell line is not representative of breast cancer cells in a patient with respect to integrin expression, a skilled practitioner would not have been motivated by these findings to treat patients with an agent capable of blocking integrin alpha 5 beta 1 interactions. Indeed, absent the teaching of the present invention, which demonstrates that breast cancer cells that survive in the bone marrow microenvironment are re-educated to re-express $\alpha5\beta1$ integrin, there is no motivation to administer to a patient an agent capable of blocking the interactions of this integrin.

In view of the above, the Nista et al. reference at the very least fails to teach a recited element of the claims. Moreover, Applicant asserts that Nista et al. specifically and prevailing scientific thought teach away from the present invention as claimed for the reasons presented herein.

In the interests of setting forth that which is known to occur during the establishment and progression of breast cancer in a mammal, Applicant presents the following brief summary. As normal ductal epithelial cells de-differentiate to become breast cancer cells, they essentially stop expressing integrins. The loss of cell surface integrin expression contributes to the ability of the breast cancer cells to detach and enter the circulation. References are submitted to support Applicant's statements pertaining to the progression of normal breast cells to breast cancer cells and the concomitant loss of integrin expression, including: Howlett et al. (1995, J Cell Science 108:1945-1957);

Jones et al. (1992, J Pathology 167:399-406); and Mechtersheimer et al. (1993, Virchows Archiv A Pathol Anat 422:203-210). These references are included in the Supplemental Information Disclosure Statement submitted herewith.

As discovered by the present inventor, the breast cancer cells that make it to the bone marrow and other distant sites via the circulatory system and survive in such microenvironments are re-educated at these sites to re-express integrins lost during malignant transformation. These integrins, and specifically integrin alpha 5 beta 1, binds fibronectin in the bone marrow and this interaction promotes the survival of the breast cancer cells that have been successfully re-educated to re-express integrin alpha 5 beta 1. The present discovery, thus, provides the first motivation to arrive at the instantly claimed methods. In short, the instant teaching is essential for an appreciation of the claimed methods because a skilled practitioner would have had no motivation to administer an agent capable of blocking $\alpha 5\beta 1$ integrin interactions without knowing that breast cancer cells learn to re-express this integrin. There is simply no motivation to administer such agents to a breast cancer patient when the prevailing thought teaches that breast cancer cells do not express $\alpha 5\beta 1$ integrin.

To emphasize further the significance of the present invention with respect to improving the prognosis of breast cancer patients, Braun at al. (2000, J Clinical Oncol 18:80-86) have shown that even after surgically removing the primary breast cancer from a patient and treating the patient with chemotherapy to eliminate cells that have metastasized and survived in the bone marrow, the cells that have metastasized survive the chemotherapy given for the very purpose of eliminating them. In a subsequent study, Braun et al. (2000, New Eng J Med 342:525-533) demonstrate that such micrometastases in the bone marrow of women with breast cancer are correlated with poor prognosis. These references authored by Braun et al. were made of record in the Information Disclosure Statement filed on or about September 18, 2007. In that the present invention teaches that metastatic breast cancer cells have been taught to re-express integrins by the bone marrow microenvironment and are kept alive by the interaction of these newly expressed integrins with fibronectin in the bone marrow, the present invention provides a novel and useful target for therapeutic intervention. Based on the present findings, therefore, agents that block the interaction of newly expressed integrins, such as $\alpha 5\beta 1$

integrin, and fibronectin will serve to eliminate these metastatic breast cancer cells and thus improve the prognosis of patients with breast cancer.

In view of the amendments to the claims and arguments presented herein, therefore, the Examiner is respectfully requested to reconsider the validity of the rejection of the claims under 35 U.S.C. §102 and withdraw the rejection.

Fees

No additional fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

Conclusion

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is earnestly solicited. In the event that there are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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Enclosures: Request for Continued Examination
Petition for a Two Month Extension of Time
Supplemental Information Disclosure Statement